Clinical trial results:
A multicenter, randomized, double-blind, 8 week study to evaluate the dose response, efficacy and safety of aliskiren in paediatric hypertensive subjects 6-17 years of age.

Summary

EudraCT number	2009-017028-22
Trial protocol	HU BE FR DE SK PL Outside EU/EEA
Global end of trial date	14 August 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CSPP100A2365

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01150357
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, +41 613241111,
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000362-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were:
• In Phase 1 (dose response phase), to evaluate the dose response of aliskiren in msSBP change at end of Phase 1 from the baseline, as measured by office BP reading, in children 6 to 17 years old with hypertension.
• In Phase 2 (placebo-controlled withdrawal phase), to evaluate pooled treatment effect of aliskiren (mid and high doses) in msSBP change at end of Phase 2 from the end of Phase 1, compared to placebo pooled from corresponding arms, as measured by office BP reading, in children 6 to 17 years old with hypertension

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Guatemala: 18
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Slovakia: 60
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 102
Worldwide total number of subjects	268
EEA total number of subjects	142

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	129
Adolescents (12-17 years)	139
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 51 centres in 8 countries.

Pre-assignment

Screening details:

A total of 334 subjects were enrolled in a screening phase of single-blind placebo wash-out period for up to a maximum of three weeks. Out of 334, 268 subjects were randomised in Phase 1 including 1 mis-randomised subject who did not receive any medication.

Period 1

Period 1 title	Dose Response Phase (Phase 1)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Randomisation data were kept strictly confidential and the identity of treatments were concealed by the use of identical study drugs. Unblinding was allowed from randomisation to database lock, except in case of subject emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Aliskiren Low (6.25/12.5/25 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kilogram(kg) to less than < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets (3.125 mg per minitablet). For the low dose arm, patients used one or more of the 6.25 mg capsule (containing 2 minitablets) once daily to reach the body-weight stratified dose of aliskiren.

Arm title	Phase 1: Aliskiren Mid (37.5/75/150 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets(3.125 mg per minitablet). For the medium dose arm, patients used one or more of the 37.5 mg capsule (containing 12 minitablets) once daily to reach

the body-weight stratified dose of aliskiren.

Arm title	Phase 1: Aliskiren High (150/300/600 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets (3.125 mg per minitablet). For the high dose arm, patients used one or more of the 150 mg capsule (containing 48 minitablets) once daily to reach the body-weight stratified dose of aliskiren.

Number of subjects in period 1[1]	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)
Started	108	54	105
Completed	107	51	102
Not completed	1	3	3
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	-	-	1
Unsatisfactory therapeutic effect	1	-	-
Protocol deviation	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 268 subjects randomised in Phase 1, 1 subject was mis-randomised who did not receive any medication and thus was not included in the safety or full analysis sets for evaluation.

Period 2

Period 2 title	Placebo-controlled withdrawal (Phase 2)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Randomisation data were kept strictly confidential and the identity of treatments were concealed by the use of identical study drugs. Unblinding was allowed only in case of subject emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes

Arm title	Phase 2: Aliskiren Low (6.25/12.5/25 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets (3.125 mg per minitablet). For the low dose arm, patients used one or more of the 6.25 mg capsule (containing 2 minitablets) once daily to reach the body-weight stratified dose of aliskiren.

Arm title	Phase 2: Placebo Low

Arm description:

Subjects received placebo capsules matching to aliskiren capsules (6.25/12.5/25 mg) once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo low
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo capsules (containing minitablets) matching in size, shape, color and number of minitablets to aliskiren capsules

Arm title	Phase 2: Aliskiren Mid (37.5/75/150 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets(3.125 mg per minitablet). For the medium dose arm, patients used one or more of the 37.5 mg capsule (containing 12 minitablets) once daily to reach the body-weight stratified dose of aliskiren.

Arm title	Phase 2: Placebo Mid

Arm description:

Subjects received placebo capsules matching to aliskiren capsules (37.5/75/150 mg) once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo mid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo capsules (containing minitablets) matching in size, shape, color and number

of minitablets to aliskiren capsules.

Arm title	Phase 2: Aliskiren High (150/300/600 mg)

Arm description:

Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.

Arm type	Experimental
Investigational medicinal product name	Aliskiren
Investigational medicinal product code	SPP100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Aliskiren dispensing capsules containing minitablets (3.125 mg per minitablet). For the high dose arm, patients used one or more of the 150 mg capsule (containing 48 minitablets) once daily to reach the body-weight stratified dose of aliskiren.

Arm title	Phase 2: Placebo High

Arm description:

Subjects received placebo capsules matching to aliskiren capsules (150/300/600 mg) once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo high
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo capsules (containing minitablets) matching in size, shape, color and number of minitablets to aliskiren capsules

Number of subjects in period 2	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)
Started	50	57	30
Completed	50	54	30
Not completed	0	3	0
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 2	Phase 2: Placebo Mid	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High
Started	21	50	52
Completed	21	49	51
Not completed	0	1	1

Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	1	1
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: Aliskiren Low (6.25/12.5/25 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kilogram(kg) to less than < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.	
Reporting group title	Phase 1: Aliskiren Mid (37.5/75/150 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.	
Reporting group title	Phase 1: Aliskiren High (150/300/600 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.	

Reporting group values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)
Number of subjects	108	54	105
Age categorical Units: Subjects			
Children 6 – 11 years	49	28	51
Adolescents 12 – 17 years	59	26	54
Age continuous Units: years			
arithmetic mean	11.9	11.6	11.8
standard deviation	± 3.27	± 3.29	± 3.5
Gender categorical Units: Subjects			
Female	35	17	39
Male	73	37	66

Reporting group values	Total		
Number of subjects	267		
Age categorical Units: Subjects			
Children 6 – 11 years	128		
Adolescents 12 – 17 years	139		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	91		
Male	176		

End points

End points reporting groups

Reporting group title	Phase 1: Aliskiren Low (6.25/12.5/25 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kilogram(kg) to less than < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.	
Reporting group title	Phase 1: Aliskiren Mid (37.5/75/150 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.	
Reporting group title	Phase 1: Aliskiren High (150/300/600 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.	
Reporting group title	Phase 2: Aliskiren Low (6.25/12.5/25 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.	
Reporting group title	Phase 2: Placebo Low
Reporting group description:	
Subjects received placebo capsules matching to aliskiren capsules (6.25/12.5/25 mg) once daily.	
Reporting group title	Phase 2: Aliskiren Mid (37.5/75/150 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.	
Reporting group title	Phase 2: Placebo Mid
Reporting group description:	
Subjects received placebo capsules matching to aliskiren capsules (37.5/75/150 mg) once daily.	
Reporting group title	Phase 2: Aliskiren High (150/300/600 mg)
Reporting group description:	
Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.	
Reporting group title	Phase 2: Placebo High
Reporting group description:	
Subjects received placebo capsules matching to aliskiren capsules (150/300/600 mg) once daily.	

Primary: Change from baseline in mean sitting systolic blood pressure (msSBP) at endpoint (Phase 1)

End point title	Change from baseline in mean sitting systolic blood pressure (msSBP) at endpoint (Phase 1)

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three sSBP measurements were used as the average sitting office blood pressure for that visit. The primary analysis was performed on the Full Analysis Set (FAS), defined as all subjects who received at least one dose of study treatment and had at least one post-baseline assessment for primary efficacy. Here, "Number of subjects analysed" signifies

subjects evaluable for msSBP at Week 4 (or LOCF) for each arm, respectively.

End point type	Primary

End point timeframe:

Baseline to endpoint (Week 4 or Last observation carried forward (LOCF))

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	53	104	
Units: millimetre(s) of mercury (mmHg)				
arithmetic mean (standard error)	-5.54 (± 0.78)	-5.42 (± 1.331)	-9.03 (± 1.008)	

Statistical analyses

Statistical analysis title	Dose-response for change in msSBP

Statistical analysis description:

The slope for change from baseline in mean sitting systolic blood pressure (msSBP) was analysed.

Comparison groups	Phase 1: Aliskiren Low (6.25/12.5/25 mg) v Phase 1: Aliskiren Mid (37.5/75/150 mg) v Phase 1: Aliskiren High (150/300/600 mg)
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	-0.07

Notes:

[1] - The null hypothesis for Phase 1 was that the slope of the dose-response curve for change from baseline in msSBP was not statistically different from zero at the end of Phase 1.

[2] - P-value was obtained from ANCOVA model fitted with weight, age, region and hypertension etiology as factors and baseline msSBP and dose ratio as covariates.

Primary: Change in mean sitting systolic blood pressure (msSBP) from Week 4 to endpoint (Phase 2)

End point title	Change in mean sitting systolic blood pressure (msSBP) from Week 4 to endpoint (Phase 2)

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three sSBP measurements were used as the average sitting office blood pressure for that visit. The primary analysis was performed on the FAS population.

End point type	Primary
End point timeframe:	
Week 4 to endpoint (Week 8 or LOCF)	

End point values	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)	Phase 2: Placebo Mid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	57	30	21
Units: mmHg				
arithmetic mean (standard error)	-0.53 (± 0.947)	-0.64 (± 1.256)	-2.59 (± 1.119)	-2.9 (± 1.481)

End point values	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	52		
Units: mmHg				
arithmetic mean (standard error)	-1.97 (± 1.071)	1.11 (± 1.185)		

Statistical analyses

Statistical analysis title	Pooled aliskiren treatment vs pooled placebo
Statistical analysis description:	
Pooled treatment effect of aliskiren (mid and high doses) compared to pooled placebo (mid and high doses) in comparison with msSBP at Week 8 from Week 4.	
Comparison groups	Phase 2: Aliskiren Mid (37.5/75/150 mg) v Phase 2: Placebo Mid v Phase 2: Aliskiren High (150/300/600 mg) v Phase 2: Placebo High
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1152 [4]
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.87
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	1.088

Notes:

[3] - The null hypothesis for Phase 2 was that the change from end of Phase 1 in msSBP was not different between the pooled aliskiren high and mid doses, and placebo pooled from corresponding arms at the end of Phase 2.

[4] - P-value was obtained from the ANCOVA model fitted with treatment, weight, age, region, and hypertension etiology as factors and msSBP at end of Week 4 as a covariate, carried out at 2-sided significance level of 0.05.

Secondary: Number of subjects with adverse events and serious adverse events from baseline to week 4 (Phase 1)

End point title	Number of subjects with adverse events and serious adverse events from baseline to week 4 (Phase 1)

End point description:

Adverse events (AEs) were defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. The analysis was performed on the Safety Sets (SAF), SAF is all subjects who received at least one dose of study treatment during phase 1 (baseline to week 4)

End point type	Secondary

End point timeframe:

From baseline to Week 4

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	54	105	
Units: Number of subjects				
AEs	30	14	37	
SAEs	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events and serious adverse events from Week 4 to Week 8 (Phase 2)

End point title	Number of subjects with adverse events and serious adverse events from Week 4 to Week 8 (Phase 2)

End point description:

AEs were defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. SAEs were defined as any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. The analysis was performed on the SAF which included all subjects who received at least one dose of study treatment during phase 2 (week 4 to week 8).

End point type	Secondary

End point timeframe:

From Week 4 to Week 8

End point values	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)	Phase 2: Placebo Mid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	57	30	21
Units: Number of subjects				
AEs	18	22	10	5
SAEs	0	0	0	0

End point values	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Number of subjects				
AEs	21	17		
SAEs	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean sitting diastolic blood pressure (msDBP) at endpoint (Phase 1)

End point title	Change from baseline in mean sitting diastolic blood pressure (msDBP) at endpoint (Phase 1)

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three sDBP measurements were used as the average sitting office blood pressure for that visit. The analysis was performed on the FAS population. Here, "Number of subjects analysed" signifies subjects evaluable for msDBP at Week 4 or LOCF for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline to endpoint (Week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	53	104	
Units: mmHg				
arithmetic mean (standard error)	-2.71 (± 0.67)	-4.05 (± 1.116)	-6.33 (± 0.793)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean sitting diastolic blood pressure (msDBP) from Week 4 to endpoint (Phase 2)

End point title	Change in mean sitting diastolic blood pressure (msDBP) from Week 4 to endpoint (Phase 2)

End point description:

Sitting blood pressure was measured using a calibrated standard sphygmomanometer after the subject remained in sitting position for 5 minutes at clinic during the visit. The repeat sitting measurements were made at 1-2 minute intervals and the mean of three sDBP measurements were used as the average sitting office blood pressure for that visit. The analysis was performed on the FAS population. Here, "Number of subjects analysed" signifies subjects evaluable for msDBP at Week 8 or LOCF for each arm, respectively.

End point type	Secondary

End point timeframe:

Week 4 to endpoint (Week 8 or LOCF)

End point values	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)	Phase 2: Placebo Mid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	57	30	21
Units: mmHg				
arithmetic mean (standard error)	1.27 (± 1.025)	-1.08 (± 1.012)	0.89 (± 1.502)	1.52 (± 1.248)

End point values	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	52		
Units: mmHg				
arithmetic mean (standard error)	0.37 (± 1.052)	1.51 (± 1.009)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean arterial pressure (MAP) at endpoint (Phase 1)

End point title	Change from baseline in mean arterial pressure (MAP) at endpoint (Phase 1)

End point description:

MAP was defined as the average arterial pressure during a single cardiac cycle. The MAP was measured as sum of diastolic blood pressure (DBP) and one third of difference between systolic blood pressure (SBP) and DBP i.e. MAP = DBP+1/3*(SBP-DBP). The analysis was performed on the FAS population. Here, "Number of subjects analysed" signifies subjects evaluable for MAP at Week 4 or LOCF for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline to endpoint (Week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	53	104	
Units: mmHg				
arithmetic mean (standard error)	-3.65 (± 0.613)	-4.51 (± 1.064)	-7.23 (± 0.771)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean arterial pressure (MAP) from Week 4 to endpoint (Phase 2)

End point title	Change in mean arterial pressure (MAP) from Week 4 to endpoint (Phase 2)

End point description:

MAP was defined as the average arterial pressure during a single cardiac cycle. The MAP was measured as sum of DBP and one third of difference between SBP and DBP i.e. MAP = DBP+1/3*(SBP-DBP). The analysis was performed on the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Week 4 to endpoint (Week 8 or LOCF)

End point values	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)	Phase 2: Placebo Mid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	57	30	21
Units: mmHg				
arithmetic mean (standard error)	0.67 (± 0.864)	-0.93 (± 0.964)	-0.27 (± 1.239)	0.05 (± 1.14)

End point values	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	52		
Units: mmHg				
arithmetic mean (standard error)	-0.41 (± 0.885)	1.37 (± 0.918)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving a positive treatment response at endpoint (Phase 1)

End point title	Percentage of subjects achieving a positive treatment response at endpoint (Phase 1)

End point description:

Treatment responders were defined as subjects with msSBP less than 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from the baseline. The analysis was performed on the FAS population. Here, "Number of subjects analysed" signifies subjects evaluable for this outcome measure at study endpoint which was week 4 or LOCF value in Phase 1.

End point type	Secondary

End point timeframe:

Baseline to endpoint (Week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	53	104	
Units: Percentage of subjects				
number (not applicable)	50.9	58.5	69.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean ambulatory systolic and diastolic blood pressure (MASBP and MADBP) at endpoint (Phase 1)

End point title	Change from baseline in mean ambulatory systolic and diastolic blood pressure (MASBP and MADBP) at endpoint (Phase 1)

End point description:

Ambulatory Blood Pressure Monitoring (ABPM) was performed over a 24-hour period using an automatic ABPM device to record the blood pressure as per study defined criteria. The subjects who were selected for this evaluation wore the ABPM device for 24 hours, returned to the clinic upon completion of the 24-hour monitoring period for removal of device and BP assessments. The ABPM device was pre-set to collect readings every 20 minutes. Mean hourly systolic and diastolic blood pressure were calculated for each subject at post dosing 1 – 24 hours. Analysis was performed in subset of FAS subjects from selected centers who consented to undergo ABPM at baseline and at Week 4 or LOCF. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline to endpoint (week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	29	65	
Units: mmHg				
arithmetic mean (standard deviation)				
MASBP (n=58, 29, 65)	-1.6 (± 6.48)	-5.9 (± 5.8)	-5.8 (± 7.15)	
MADBP (n=58, 29, 65)	-1.1 (± 5.33)	-4.4 (± 4.41)	-4.9 (± 6.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean ambulatory systolic blood pressure (MASBP) during day and night at week 4 (Phase 1)

End point title	Change from baseline in mean ambulatory systolic blood pressure (MASBP) during day and night at week 4 (Phase 1)

End point description:

ABPM was performed over a 24-hour period using an automatic ABPM device to record the blood pressure as per study defined criteria. Day time was defined as the average of the hourly means between 6 am and 10 pm while the night time mean was the average of the hourly means between 10

pm and 6 am. Analysis was performed in subset of FAS subjects from selected centers who consented to undergo ABPM at baseline and at Week 4. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline to week 4

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	29	65	
Units: mmHg				
least squares mean (standard error)				
Day time (n= 58, 29, 65)	-2.72 (± 1.031)	-6.76 (± 1.381)	-6.56 (± 0.95)	
Night time (n= 57, 29, 65)	-2.55 (± 1.035)	-4.67 (± 1.381)	-4.9 (± 0.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean ambulatory blood pressure (MABP) in dipper subjects at endpoint (Phase 1)

End point title	Change from baseline in mean ambulatory blood pressure (MABP) in dipper subjects at endpoint (Phase 1)

End point description:

ABPM was performed over a 24-hour period using an automatic ABPM device to record the blood pressure as per study defined criteria. Dippers were defined as those subjects in whom there was a decrease in mean night time (6pm – 6am) ABPM more than or equal to (≥) 10% as compared to average daytime (6am –6pm) ABPM. Analysis was performed in subset of FAS subjects from selected centres who consented to undergo ABPM at baseline and at Week 4 or LOCF. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline to endpoint (week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	21	47	
Units: mmHg				
arithmetic mean (standard deviation)				
MASBP	-1.2 (± 6.18)	-4.6 (± 5.47)	-6 (± 6.19)	

MADBP	-0.6 (± 5.78)	-3.6 (± 4.19)	-5.3 (± 5.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean ambulatory blood pressure (MABP) in non-dipper subjects at endpoint (Phase 1)

End point title	Change from baseline in mean ambulatory blood pressure (MABP) in non-dipper subjects at endpoint (Phase 1)

End point description:

ABPM was performed over a 24-hour period using an automatic ABPM device to record the blood pressure as per study defined criteria. Non-dippers were defined as those subjects in whom there was a decrease in mean night time ABPM less than 10% as compared to average daytime ABPM. Analysis was performed in subset of FAS subjects from selected centers who consented to undergo ABPM at baseline and at Week 4. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline to endpoint (Week 4 or LOCF)

End point values	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	8	18	
Units: mmHg				
arithmetic mean (standard deviation)				
MASBP	-2.6 (± 7.21)	-9.3 (± 5.54)	-5.2 (± 9.39)	
MADBP	-2.3 (± 4.05)	-6.7 (± 4.45)	-3.9 (± 7.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All adverse events reported in this record are from date of First Subject First Treatment until LSLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Phase 1: Aliskiren Low (6.25/12.5/25 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kilogram(kg) to less than < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.

Reporting group title	Phase 1: Aliskiren Mid (37.5/75/150 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.

Reporting group title	Phase 1: Aliskiren High (150/300/600 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.

Reporting group title	Phase 2: Aliskiren Low (6.25/12.5/25 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (6.25/12.5/25 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 6.25 mg; ≥50 kg and < 80 kg received 12.5 mg and ≥ 80 kg and ≤ 150 kg received 25 mg of aliskiren.

Reporting group title	Phase 2: Placebo Low

Reporting group description:

Subjects received placebo capsules matching to aliskiren capsules (6.25/12.5/25 mg) once daily.

Reporting group title	Phase 2: Aliskiren Mid (37.5/75/150 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (37.5/75/150 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 37.5 mg; ≥50 kg and < 80 kg received 75 mg and ≥ 80 kg and ≤ 150 kg received 150 mg of aliskiren.

Reporting group title	Phase 2: Placebo Mid

Reporting group description:

Subjects received placebo capsules matching to aliskiren capsules (37.5/75/150 mg) once daily.

Reporting group title	Phase 2: Aliskiren High (150/300/600 mg)

Reporting group description:

Subjects received body-weight stratified dose of aliskiren capsules (150/300/600 mg) once daily. Subjects whose body weight ≥ 20 kg to < 50 kg received 150 mg; ≥50 kg and < 80 kg received 300 mg and ≥ 80 kg and ≤ 150 kg received 600 mg of aliskiren.

Reporting group title	Phase 2: Placebo High

Reporting group description:

Subjects received placebo capsules matching to aliskiren capsules (150/300/600 mg) once daily.

Serious adverse events	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 54 (0.00%)	1 / 105 (0.95%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 108 (0.00%)	0 / 54 (0.00%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 108 (0.00%)	0 / 54 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 108 (0.00%)	0 / 54 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Placebo Mid	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	2 / 50 (4.00%)	0 / 52 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 21 (0.00%)	0 / 50 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	1 / 50 (2.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 21 (0.00%)	1 / 50 (2.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1: Aliskiren Low (6.25/12.5/25 mg)	Phase 1: Aliskiren Mid (37.5/75/150 mg)	Phase 1: Aliskiren High (150/300/600 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 108 (10.19%)	6 / 54 (11.11%)	14 / 105 (13.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 108 (4.63%)	3 / 54 (5.56%)	7 / 105 (6.67%)
occurrences (all)	6	3	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 108 (2.78%)	3 / 54 (5.56%)	2 / 105 (1.90%)
occurrences (all)	3	3	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 54 (0.00%)	1 / 105 (0.95%)
occurrences (all)	1	0	1
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 108 (0.00%)	0 / 54 (0.00%)	0 / 105 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 108 (2.78%)	3 / 54 (5.56%)	5 / 105 (4.76%)
occurrences (all)	3	3	6

Non-serious adverse events	Phase 2: Aliskiren Low (6.25/12.5/25 mg)	Phase 2: Placebo Low	Phase 2: Aliskiren Mid (37.5/75/150 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 50 (16.00%)	7 / 57 (12.28%)	7 / 30 (23.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 50 (8.00%)	3 / 57 (5.26%)	1 / 30 (3.33%)
occurrences (all)	4	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	3 / 57 (5.26%)	2 / 30 (6.67%)
occurrences (all)	1	3	2
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 57 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)	2 / 57 (3.51%)	3 / 30 (10.00%)
occurrences (all)	3	2	4

Non-serious adverse events	Phase 2: Placebo Mid	Phase 2: Aliskiren High (150/300/600 mg)	Phase 2: Placebo High
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)	9 / 50 (18.00%)	5 / 52 (9.62%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	4 / 50 (8.00%)	3 / 52 (5.77%)
occurrences (all)	2	5	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 50 (0.00%)	0 / 52 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 21 (0.00%)	2 / 50 (4.00%)	0 / 52 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 50 (0.00%)	0 / 52 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	4 / 50 (8.00%)	2 / 52 (3.85%)
occurrences (all)	1	4	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2010	• Obviated requirement to collect pregnancy outcomes for partners of subjects who took study drug • Required echocardiography to be performed at baseline, prior to the administration of study drug • Addition of medical history to the assessment schedule
05 April 2010	• Clarified age at randomization • Clarified echocardiography requirements • Added 4 study visits for the purpose of collecting weekly trough BP • Addition of trough PK collection at Visit 4. • Addition of glucose to clinical chemistry parameters • Removal of alkaline phosphotase from the clinical chemistry parameters • Addition of sodium, potassium, chloride and BUN collection at Visit 2
29 September 2010	Prohibited treatment with itraconazole after start of the single-blind placebo run-in period
24 June 2013	Reduced the minimum requirement of randomized subjects with secondary hypertension to 10%

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported